

Accepted Manuscript

Hypersensitivity reactions with prolonged infusions of beta-lactams?

Fjeld Hilde, Stylianou Eva

PII: S1198-743X(18)30599-8

DOI: [10.1016/j.cmi.2018.08.021](https://doi.org/10.1016/j.cmi.2018.08.021)

Reference: CMI 1424

To appear in: *Clinical Microbiology and Infection*

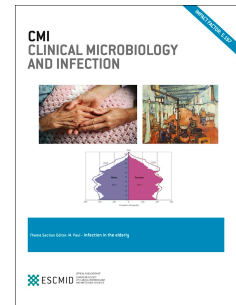
Received Date: 4 July 2018

Revised Date: 24 August 2018

Accepted Date: 25 August 2018

Please cite this article as: Hilde F, Stylianou E, Hypersensitivity reactions with prolonged infusions of beta-lactams?, *Clinical Microbiology and Infection* (2018), doi: 10.1016/j.cmi.2018.08.021.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



Hypersensitivity reactions with prolonged infusions of beta-lactams?

To the Editor,

The use of prolonged (extended or continuous) infusions of beta-lactams was a hot topic at the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) 2018 in Madrid. Prolonged infusion dosing of beta-lactam antibiotics is being increasingly used in intensive care units in an attempt to optimise treatment with this most commonly used class of antibiotics, whose effectiveness is challenged by increasing resistance rates. We agree on the pharmacokinetic and pharmacodynamics arguments for using these agents as prolonged infusions. However, when applying prolonged infusions, there are several important issues that need to be considered.

We are concerned about the degradation and/or transformation products of beta-lactams which may form in solution, and the possible increased risk of hypersensitivity reactions. The majority of studies evaluating prolongation of the infusion time, did not report on possible adverse events (1). Several penicillins (Penicillin G, methicillin, ampicillin, carbenicillin, ticarcillin) are reported to form antigenic degradation products and polymer conjugation products during *in vitro* storage (2). Stored solutions of the narrow spectrum beta-lactam benzylpenicillin (Penicillin G) have been reported to give sensitization of lymphocytes and formation of anti-penicilloyl IgG antibodies. When freshly prepared penicillin solutions were administered these effects were prevented (3). Increased frequency of adverse reactions following intravenous administration of stored benzylpenicillin solutions, including rash and eosinophilia, was reported in a study published in 1984, where freshly prepared bolus was compared to stored solutions given as infusions (4). The so-called “stored solutions” of benzylpenicillin were stored for up to 36 hours, which is a clear exaggeration of the wanted prolonged infusion time in clinical practice. These effects of storage of benzylpenicillin solutions have to our knowledge not been confirmed by later studies. Narrow spectrum agents as benzylpenicillin are not widely used anymore, and benzylpenicillin is often used with a buffer in settings where longer infusion times are necessary. We are still concerned that the subject of hypersensitivity related to time in solution is relevant, both for narrow spectrum beta-lactams and for more broad-spectrum beta-lactams. Mouton and Vinks briefly discussed hypersensitivity and time in solution for beta-lactams in an article from 2007 (5), but the subject is seldom mentioned nowadays.

As hypersensitivity may be related to time in solution, hence stability, we will also discuss some stability data. The issue becomes highly relevant when longer infusion time than recommended in the product information is desired. Degradation of beta-lactams are among others dependent on temperature, concentration, and the solution used for diluting. Microbiological integrity of the product is also crucial, but will not be discussed in this letter. Few beta-lactams are stable enough to be given as 24 hour infusions. A reference manual reports that meropenem for intravenous infusion is stable for 1 hour at temperatures of up to 25°C in sodium chloride 0.9 %, at concentrations of 1 to 20 mg/mL. The same reference manual also reports that solutions containing meropenem 10 and 20 mg/mL has been found stable for 12 hours at 25°C (6). Stability studies are often small in size, and are performed and analyzed in a number of ways. As the study designs used are quite heterogeneous, the results often vary from publication to publication, and are therefore often challenging to use as a base for choosing the optimal infusion time. Unless a reference manual is at hand, the information found will often be inadequate. For beta-lactams it is also crucial to know if the data reported is with or without buffer added. Some piperacillin-tazobactam products are formulated with buffer, while others are not. The consequences of lack of chemical and physical stability for a drug are among others less effect, and hence no clinical cure.

Implementation of prolonged infusion of beta-lactam antibiotics is fraught with a number of important practical issues that, when not considered, may jeopardise the therapy and be harmful for the patient.

The information on possible increased risk of hypersensitivity reactions related to time in solution is complex to evaluate and might be a good area for future research. We highly recommend collaboration to find solutions on this important matter, instead of professionals one-by-one interpreting literature on chemical stability and adverse reactions. We would also like to encourage inclusion of data on infusion times and adverse events in a systematic way in publications. Comments on the hypersensitivity issue related to time in solution for beta-lactams will be very appreciated.

Transparency declaration:

- Mrs. Fjeld and Dr. Stylianou have nothing to disclose.
- No external funding was received for the manuscript.
- Contribution to the manuscript:
 - o Mrs. Fjeld: Idea, literature search, data interpretation, writing
 - o Dr. Stylianou: Literature search, data interpretation, writing

References:

1. Vardakas KZ, Kalimeris GD, Triarides NA, Falagas ME. An update on adverse drug reactions related to beta-lactam antibiotics. Expert opinion on drug safety. 2018;17(5):499-508.
2. McEvoy GK, editor. Natural Penicillins General Statement. The AHFS Drug Information (online). <http://www.medicinescomplete.com/> (Access date: 22th of August 2018).
3. Neftel KA, Walti M, Spengler H, de Weck AL. Effect of storage of penicillin-G solutions on sensitisation to penicillin-G after intravenous administration. Lancet. 1982;1(8279):986-8.
4. Neftel KA, Walti M, Schulthess HK, Gubler J. Adverse reactions following intravenous penicillin-G relate to degradation of the drug in vitro. Klin Wochenschr. 1984;62(1):25-9.
5. Mouton JW, Vinks AA. Continuous infusion of beta-lactams. Curr Opin Crit Care. 2007;13(5):598-606.
6. McEvoy, GK, editor. Handbook on Injectable Drugs. In: Medicines Complete. Meropenem. <http://www.medicinescomplete.com/> (Access date: 13th of August 2018). [